Current Colorectal Cancer Reports (2019) 15:45–52
https://doi.org/10.1007/s11888-019-00432-4

SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (S HUERTA, SECTION EDITOR)

Current Trends in Colorectal Cancer Screening

Divya B. Bhatt[1] · Valerie-Sue Emuakhagbon[2]

Published online: 11 April 2019

Abstract

Purpose of Review The following review is to assess the current methods, both non-invasive and invasive, in colorectal cancer screening and discuss novel screening techniques.

Recent Findings Colorectal cancer continues to affect millions of people across the world. Through increased and widespread adoption of various screening methods, the rates of colon cancer-related deaths are decreasing. However, this decline has not been observed worldwide, possibly due to the lack of widespread screening adoption. Although there are many methods for screening colorectal cancer, colonoscopy remains the gold standard, due to high sensitivity and specificity as well as the ability to immediately sample or remove concerning tissue. Blood-based molecular testing is the most recent advancement in colorectal cancer screening; however, it has a significantly lower sensitivity and specificity when compared to other methods. However, with continued investigation, blood-based molecular testing may change how we screen for colorectal cancer in the near future.

Summary Several options for colorectal cancer screening exist today. Colorectal cancer screening methods and techniques have improved over the last several decades. These improvements have helped to decrease the rates of colorectal cancer-related deaths, most notably in the USA. Various organizations have provided a list of recommendations and suggested screening agendas, which will be reviewed in this discussion.

Keywords Colorectal cancer · Screening · Colonoscopy · Sigmoidoscopy · FIT · FOBT · Colonography · Stool DNA

Introduction

Worldwide, colorectal cancer (CRC) continues to account for a significant cause of morbidity and mortality. As the third most commonly diagnosed cancer, it has an incidence of approximately 9% and it is the fourth most common cause of cancer-related deaths [1]. In the USA, the incidence of CRC and the mortality have remained relatively constant over the past 18 years, with a mean of 143,291 ± (SD) 5860 and 52,169 ± 2870 [data obtained from Cancer Statistics from 2002 to 2018 by Jemal et al. [2] (Fig. 1)]. While there has been a moderate reduction in the mortality from CRC, there is substantial room for improvement.

One of the most important aspects that could reduce mortality from CRC is early screening. For instance, from 2007 to 2013, the incidence of colorectal cancer stage by stage was 23% (stage I), 24.5% (stage II), 24.7% (stage III), and 20.0% (for stage IV) at the time of diagnosis [3]. The 5-year survival for colorectal cancer stage by stage from 2007 to 2013 was noted to be 88.1% (stage I), 80.1% (stage II), 65.8% (stage III), and 12.6% (stage IV) [2]. The staggering number of patients presenting with metastatic disease demonstrates the paucity of current screening adherence.

An ideal screening test must be both highly sensitive and specific. Generally, tests with high sensitivity suggest disease (but suffer from poor specificity), and highly specific tests are diagnostic [4]. Furthermore, a good screening test must be cost-effective; a lower level of income correlates with lower rates of screening for colorectal cancer [5]. More importantly, screening test must be associated with good compliance. Despite screening standards, a test with an excellent sensitivity and specificity will not reduce mortality if patients are unwilling to be tested.

This article is part of the Topical Collection on *Surgery and Surgical Innovations in Colorectal Cancer*

✉ Valerie-Sue Emuakhagbon
valerie-sue.emuakhagbon@UTSouthwestern.edu

[1] VA North Texas Health Care System, Department of Gastroenterology and Hepatology, University of Texas Southwestern Medical Center, Dallas, TX, USA

[2] VA North Texas Health Care System, Department of Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA

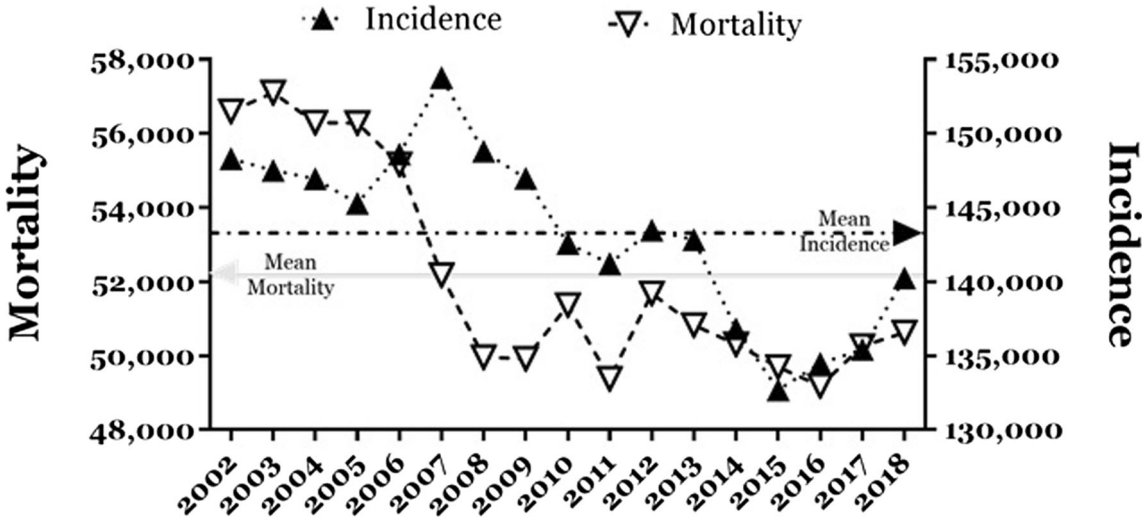

Fig. 1 Incidence and mortality for CRC in men and women in the USA

Colonoscopy is the gold standard for the detection and prevention of colorectal cancer [6]. However, it is invasive with associated risk and can be costly, deterring many patients from using colonoscopy as regular screening. As of 2014, only 60.8% of American adults between the ages of 50 and 64 underwent CRC screening of any kind, and one third of Americans have never been screened [7, 8]. Randomized controlled trials have shown that offering non-invasive testing such as fecal immunohistorchemical testing (FIT) increased the rate of CRC screening [9]. It is clear from the current evidence that screening for colorectal cancer is extremely underutilized [10].

The following review discusses all the current screening tests for colorectal cancer. We will focus on non-invasive and novel screening modalities that might lead to higher compliance. Potential implications increasing compliance, such as cost, will also be addressed.

Current Recommendations

In general, a test should only be performed if it is going to change the management of an individual. As such, screening for colorectal cancer should be performed on a patient healthy enough to undergo treatment, without a prohibitive risk of surgical intervention. Current recommendations in the USA indicate that everyone who is asymptomatic and average-risk (Table 1), aged 50 to 75, should undergo colorectal cancer screening. This recommendation emanates from a reduction in mortality from this strategy and the median age of diagnosis of 68 years of age [10]. Because the risk of colorectal cancer increases with age, this is the most important risk factor for the asymptomatic patient. Several organizations have developed screening guidelines. These include the US Preventive Services Task Force (USPSTF) [10], American College of Gastroenterology (ACG) [6], American College of Physicians (ACP) [11], and the American Cancer Society [12]. Table 2 summarizes the latest recommendations each set of guidelines.

The ACS guidelines have been recently updated (2018) following the last update a decade prior [12]. To date, this is the most up to date and comprehensive review of guidelines for colorectal cancer screening and includes recommendation and reviews of other societies. According to the new recommendations, the evidence is considered either *strong* or *qualified* based on GRADE guidelines [13]. The difference is that qualified recommendations cannot uniformly assess the risk benefit outcome of the intervention and must be further determined on an individual basis. Additionally, the financial burden of the recommendations is not assessed, but the authors recognize the importance and impact that this might have in the American population. The recent recommendations of the ACS are depicted in Tables 3 and 4. The difference from prior recommendations in this update is the *qualified* recommendation to begin screening at age 45 for average, non-symptomatic individuals.

The USPSTF concludes a screening benefit for average-risk, asymptomatic adults aged 50–75. Patients aged 75–85

Table 1 Description of non-average-risk individuals

Non-average-risk individuals need different screening schedules
1. History of Lynch syndrome
2. History of familial adenomatous polyposis
3. History of inflammatory bowel disease
4. History of polyps
5. History of previous colorectal cancer
6. First degree relatives with colorectal cancer

Table 2 Society guideline regarding colorectal cancer screening

	ACG (reference)	ACP (reference)	USPSTF (reference)
FOBT	Q 1 year	Q 1 year	Q 1 year
FIT	Q 1 year	Q 1 year	Q 1 year
Stool DNA	N/A	N/A	Q 1–3 years
CT colonography	Q 5 years	N/A	Q 5 years
Flexible sigmoidoscopy	Q 5–10 years	Q 5 years	Q 5–10 years
Colonoscopy	Q 10 years	Q 10 years	Q 10 years

FOBT fecal occult blood test, *FIT* fecal immunochemical testing, *CT* computed tomography

must be assessed on an individual basis. Racial/ethnic background as well as male gender must be evaluated in the screening schedules. A review of the currently available screening tests is included: guaiac-based fecal occult blood test (gFOBT), FIT, FIT-Check, FIT-DNA and direct visualization techniques, CT colonography, and serology tests. These are also reviewed in other guidelines, and the salient aspects of each test are discussed below. Starting age of screening is discussed with the best evidence suggesting that 50–75 years of age has the highest yield of lowering mortality (asymptomatic, average-risk patient). Screening at age 45 and specific racial groups is also addressed. Screening intervals are discussed as well in this set of guidelines (Table 2). The risk of complications from each procedure is mentioned in this manuscript. However, the more invasive the test (i.e., colonoscopy with biopsy), the more the complication rate (risk). The harm of non-invasive tests has to do with a follow-up colonoscopy if the test is positive. The risk for colonoscopy is 4 perforations and 8 major bleeding episodes per 10,000 screening colonoscopies, which is higher 14 and 24 if the procedure is performed as a follow-up for an abnormal finding [14].

In 2009, the screening guidelines from the ACG were updated. The updates included separating screening modalities into two main groups: cancer prevention versus cancer detection. The modalities within the cancer prevention modalities have a higher capability of imaging both cancers and polyps. Whereas the cancer detection modalities have a lower sensitivity for polyps and cancers when compared to the cancer prevention group. Nonetheless, the society offers both cancer prevention and detection as screening recommendations. It is important to note that the ACG recommends colonoscopic evaluation to start at age 50. They also note that screening should start at age 45 in the African American population. For patients who refuse colonoscopy, the preferred cancer detection test modality is fecal immunohistorchemical testing (FIT) which should be performed annually. Table 5 summarizes the guidelines [6].

The ACP recommends age 50 years as the starting age for colorectal cancer screening in average-risk patient. However, they make important note that screening options and age of screening onset should be individualized for each patient. Similar to the previously mentioned societies, the ACP recommends colonoscopy as the preferred screening modality. When choosing a screening modality, it is important to choose a technique that is cost-effective. Table 6 summarizes the guidelines proposed by the ACP, in regard to effectiveness, cost, and frequency [9].

Table 3 American Cancer Society Recommendation Guidelines (2018)

CRC screening options	Frequency
Stool-based tests	
FIT	Annual
FOBT	Annual
DNA test	Q 3 years
Structural tests	
Colonoscopy	Q 10 years
CT colonography	Q 5 years
Flexible sigmoidoscopy	Q 5 years

FIT fecal immunohistochemical test, *FOBT* fecal occult blood test, *CT* computed tomography

Screening Methods

Endoscopy

CRC is thought to occur due to a "multihit" hypothesis [15]. In 1978, Hill proposed that an unknown environmental agent caused the growth of precancerous lesions, or polyps, in individuals with a genetic predisposition [16]. A decade later, Vogelstein and colleagues demonstrated that polyps with size,

Table 4 American Cancer Society Recommendation Guidelines (2018)

Qualified recommendations
- Screening age starts at 45 years
- Screening age ends at 75 years
- Screening should be individualized based on patient and provided between ages 76 and 85 years
- No screening after 85 years

Strong recommendations
- Screening age starts at 50 years

Table 5 American College of Gastroenterologist Recommendation Guidelines (2009)

Cancer prevention	Cancer detection
Colonoscopy Q 10 years*	FIT Q 1 year*
Flexible sigmoidoscopy Q 5–10 years	Hemoccult Q 1 year
CT colonography Q 5 years	Fecal DNA Q 3 years

*Preferred modality

villous features, and dysplasia had an increased risk of developing CRC [17]. Colonoscopy was developed in 1969 to excise and remove precancerous polyps and thus remove the risk for CRC [18]. In the last 50 years, major advances have been made to make endoscopy, e.g., colonoscopy and flexible sigmoidoscopy, safer, more effective, and better tolerated. More recently, flexible sigmoidoscopy has become less commonly used, as evidence shows that right-sided colonic lesions are more frequently missed [19].

Unlike other screening methods, endoscopy is both diagnostic and therapeutic: once visualized, polyps can be biopsied and/or removed. Thus, any non-invasive screening method, if positive, would indicate a need for colonoscopy. As an invasive test frequently requiring sedation, endoscopy carries risks including bleeding, infection, perforation, cardiopulmonary events from sedation, missed lesions, and even death; the risk of serious adverse events is approximately 2.8 per 1000 procedures [20]. These risks are small, but significant enough to cause concern among individuals. Furthermore, endoscopy is expensive (Medicare reimbursement for diagnostic colonoscopy was $195 in 2017 [21]) and requires a bowel preparation for adequate polyp detection, which most patients find inconvenient and uncomfortable. These factors likely contribute to the low level of adherence to recommended screening.

Stool-Based Screening

Several fecal tests have been developed to screen for CRC. Stool-based testing relies on the premise that abnormal cells are exfoliated and shed into the stool, thus allowing for the detection of specific markers [22, 23].

Stool Hemoglobin Testing

The guaiac-based fecal occult blood test (gFOBT) was recommended by the US Preventive Services Task Force in 1996 as a non-invasive screening mechanism for CRC after multiple population-based studies showed a clear reduction in mortality [24, 25]. The gFOBT is traditionally a three-sample test and detects the presence of heme when hydrogen peroxide oxidizes guaiac to form a blue color [26]. However, this can be affected by ingestion of dietary hemoglobin, antioxidants, and other substances. Although annual testing has a sensitivity of 90% over a 5-year period [27], it has been shown that the sensitivity may be attributed to false positive results (as high as 10%) from other causes of occult bleeding [28]. As a result of these limitations, fecal immunochemical testing (FIT) was developed.

FIT detects fecal human hemoglobin using antibodies that bind to the intact globin component. Unlike gFOBT, FIT requires one stool sample and does not require any dietary restrictions. Compared to colonoscopy, FIT sensitivity and specificity for CRC were 71% and 94%, respectively [29]. There are multiple qualitative and quantitative versions of FIT: while the qualitative test provides a positive or negative test result based on a certain threshold, the quantitative test provides a fecal hemoglobin concentration [26]. FIT accuracy in average-risk asymptomatic participants has been shown to be highly variable depending on the threshold value used; a cutoff value less than 20 μg/g had 89% sensitivity and 91% specificity for CRC compared to tests that used higher thresholds [29].

Stool DNA Testing

Stool DNA (sDNA) panels were developed to evaluate for specific tumor markers known to be associated with CRC. Syngal et al. analyzed stool samples of patients newly diagnosed with CRC or advanced precancerous polyp (APP) before treatment, 1–3 months after surgical resection, and 6–9 months after resection [30]. Stool samples were analyzed using the multitarget DNA assay panel (MTAP) consisting of 23 markers, including p53 mutations, K-ras, APC, a microsatellite instability marker, and a marker of disordered apoptosis. MTAP sensitivity was 63% for CRC and 26% for APP [30].

Table 6 American College of Physicians Recommendation Guidelines (2012)

Modality	Sensitivity	Specificity	Cost	Interval
FOBT	Variable	Variable	Low	Annual
FIT	Variable	Variable	Medium	Annual
Stool DNA	Variable	High	High	Unknown
Double contrast barium enema	Low	Low	Low	Q 5 years
CT colonography	Medium	Medium	High	Q 5 years
Flexible sigmoidoscopy	Medium	Medium	High	Q 5 years
Colonoscopy	High	High	High	Q 10 years

Interestingly, a positive stool DNA test appeared to correlate with the presence of tumor, as most stool samples after resection were negative [30]. The sDNA panel was reformulated by Exact Sciences (Exact Sciences, Madison, WI) to include point mutations in K-ras, hypermethylated BMP3 and NDRG4, the β-actin gene (for DNA quantity control), and a human hemoglobin immunochemical assay [31]. In the screening trial, Imperiale et al. showed that Cologuard (Exact Sciences, Madison WI) was more sensitive than FIT for CRC (92.3% compared to 73.8%), although it was less specific (86.6% versus 94.9%) [32]. Unlike FIT, sensitivity did not vary with CRC stage or location. Furthermore, Cologuard had a sensitivity of 42.4% compared to FIT sensitivity of 23.8% for APP [32]. The Food and Drug Administration approved Cologuard for average-risk CRC screening in 2014, with a recommended screening interval of 3 years. Currently, the Center for Medicare and Medicaid Services (CMS) reimbursement for Cologuard is $493 compared to $23 for FIT [33]. However, Prince et al. showed that using Cologuard improved compliance in previously non-compliant Medicare patients [34•].

Stool Protein Testing

M2-pyruvate kinase (M2PK), an isoenzyme of pyruvate kinase, plays a crucial role in glycolysis during tumor growth by shifting cellular metabolism to aerobic glycolysis [35]. The dimeric form of M2PK is induced by different oncoproteins and is most commonly found in tumorigenesis [36]. As a result, M2PK stool levels are elevated in CRC, although high levels can also be seen in acute and chronic inflammatory bowel disease (IBD). The sensitivity for M2PK for CRC, with a cutoff value of 4 U/mL, is 79%, and the specificity is 73 [36–38]. The test is available both in ELISA and immunochromatographic form [38], and the cost of M2PK is similar to FIT ($25) [36]. However, further population studies are needed to fully characterize the potential of this test.

Fecal calprotectin has also been studied as a biomarker for CRC screening. However, the Norwegian Colorectal Cancer Prevention Trial showed that calprotectin had both lower sensitivity for both CRC and APP and a lower specificity [39]. Widlak et al. showed that FIT and fecal calprotectin, used in combination, was not superior to FIT alone [40]. Due to these findings, using fecal calprotectin has fallen out of favor.

Blood-Based Screening

Ideally, screening via blood samples would identify mutations that predispose an individual to increased CRC risk. Examples of effective serum screening tests include the RET proto-oncogene for multiple endocrine neoplasia (MEN) and the BRCA genes for breast cancer. These markers are the result of germ line mutations. Currently, patients may undergo genetic screening for mutations including familial adenomatous polyposis or Lynch syndrome if considered high risk [15, 41–43]. However, in the USA, 95% of CRC occurs de novo, characterized by somatic mutations.

Blood tests may be more acceptable to patients and may increase screening uptake overall [44, 45]. However, testing for biomarkers of neoplasia would indicate vascular invasion or, at the very least, an inflammatory reaction leading to the immune presentation of these markers [22, 23]. Therefore, these tests are very limited for clinical implementation for screening purposes.

DNA-Based Tests

Methylated septin9, a gene involved in cell cycle control and cytokinesis, has been studied as a potential biomarker for CRC [46–48]. The SEPT9 DNA methylation assay was subsequently developed as a possible CRC screening tool. The SEPT9 assay was included in DNA extraction from plasma, bisulfite conversion and purification, quantification by polymerase chain reaction (PCR), and measurement of Septin9 methylation [46]. Initial trials were promising, and the Food and Drug Administration approved SEPT9 for CRC screening in 2016. However, the PRESEPT trial showed that SEPT9 had a sensitivity of 48.2% and a specificity of 91.5% for CRC, with a sensitivity of 11.2% for APP [49]. Ahlquist et al. compared SEPT9 to sDNA and found that SEPT9 had a lower sensitivity and higher false positive rate compared to sDNA [22]. Jin et al. showed that the second-generation SEPT9 test may have improved significantly, with sensitivity and specificity similar to FIT [50, 51]. Given conflicting data, the role of SEPT9 in CRC screening is yet unclear.

RNA-Based Tests

It is known that RNA expression becomes increasingly dysregulated in cancer growth [52]. Marshall et al. analyzed messenger RNA from subjects with CRC and controls, developing a seven-gene biomarker assay for CRC screening [53]. The assay is composed of seven genes (ANXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1, and IL2RB) and has similar sensitivity and specificity to first-generation SEPT9 [53, 54•]. Marketed as ColonSentry by GeneNews Ltd. (Richmond Hill, Ontario, Canada), it is approved as a risk assessment tool rather than a screening tool for CRC [55].

MicroRNAs are small, non-coding RNAs. Several microRNA tests are also being developed for CRC screening. Wang et al. evaluated plasma miR-409-3p, miR-7, and miR-93 as potential circulating biomarkers that could be used to detect CRC of all stages [56]. MicroRNAs appear to have a stronger correlation to metastasized CRC, however can be detected prior to metastasis. Multiple microRNAs have been associated with CRC; however, again, the sensitivity and

specificity appear to be lower than stool-based testing and application for screening is not well defined [31, 57]. Circular RNAs, non-coding RNAs with a closed-loop structure, may act as a target for microRNAs associated with CRC; however, at this point, the clinical application is hard to define [58].

Protein-Based Tests

Chen et al. assessed the diagnostic properties of 92 tumor-associated biomarkers, using 35 cases of CRC and 54 controls, and found 17 biomarkers that were significantly different in CRC versus controls [59]. The same group evaluated autoantibodies against tumor-associated antigens and found that a combination of four autoantibodies (anti-MAGEA4, anti-TP53, anti-IMPDH2, anti-MDM2) created a panel with low sensitivity of 26%, however high specificity of 90% for CRC, with 20% detection of APP [60]. Other tested immunoassays have not shown superiority to stool testing methods [61, 62]. These biomarkers may play an adjunct role to stool-based testing; however, further studies (population-based) should be undertaken.

Image-Guided Non-invasive Screening

Imaging modalities have emerged as non-invasive ways to detect polyps and CRC. However, similar to colonoscopy, these techniques require bowel preparation, and are costly. Double-contrast barium enema has largely been replaced by CT colonography (CTC) as a radiologic alternative to colonoscopy [6]. The sensitivity of CTC to detect adenomas 1 cm or greater in size ranges from 67 to 94%, and the specificity ranges from 86% to 98% [14]. However, data for smaller or flat polyps is poor. Patients still have to take a bowel preparation, and colonoscopy is recommended if a polyp is found. CTC carries a lower risk of perforation, but radiation exposure should also be weighed [61, 63]. Currently, CTC is recommended at 5-year intervals for average-risk patients [6]. Published data regarding the impact of CTC as effective CRC screening is yet lacking.

Novel Techniques

Check-Cap Ltd., an Israel-based company, is developing a preparation-free capsule-based screening method for CRC. The C-scan® system uses an ultra-low-dose X-ray capsule, an integrated recording system, and software that purportedly will create a three-dimensional map of the colon [64••]. The FDA has conditionally approved the company's investigational device exemption (IDE) application to start a US pilot study, the company announced in September 2018.

Another Israel-based company, Outsense, has created a sensor that clips onto the toilet bowl, featuring a camera and a data acquisition device connected to a mobile device app. It monitors occult blood, among other as yet unknown biomarkers. Per the website, the company has received the European Innovation Council's Small and Moderate Enterprise Feasibility Support (Phase I) grant in 2017 [65].

Machine learning is also being integrated into CRC screening. Hornbrook et al. demonstrated the use of a statistical detection model (ColonFlag®, marketed by Medial EarlySign Inc., Kfar Malal, Israel) to alert providers to patients who might be at increased risk for CRC [66]. Urban et al. used convolutional neural networks, a deep learning model for image analysis, to improve polyp detection in real time during colonoscopy [67••]. It is very possible that the next 5 years will bring new and exciting technologies, improving CRC screening and detection.

Conclusions

Early detection of colorectal cancer is pivotal in the management of this malignancy. Multiple factors have to be included in the choice of a test, including patient's educational background, test characteristics, cost, frequency, and primary care physician recommendations [68–73]. Overall, the best test is the one with the highest rate of compliance; the more people tested, the more likelihood to find affected patients. It has been demonstrated that offering choices with regard to screening increases compliance [74]. Furthermore, it is clear that screening for colorectal cancer is underutilized, and efforts to increase screening would benefit overall survival.

While most patients would prefer non-invasive testing, or testing without a bowel preparation, colonoscopy remains the gold standard. Currently, imaging modalities allow us to visualize polyps > 1 cm and early tumors and may be the best screening alternative to colonoscopy for average-risk patients. Stool and blood screening options are promising, but many require more development and testing prior to widespread use. Perhaps, a combination of non-invasive tests will be suitable for screening in the near future.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22(4):191–7.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.
3. Cronin KA, et al. Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. Cancer. 2018;124(13):2785–800.
4. Maxim LD, Niebo R, Utell MJ. Screening tests: a review with examples. Inhal Toxicol. 2014;26(13):811–28.
5. Simkin J, et al. Differences in colorectal cancer screening rates across income strata by levels of urbanization: results from the Canadian Community Health Survey (2013/2014): Can J Public Health; 2018;110(1):62–71.
6. Rex DK, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104(3):739–50.
7. Shapiro JA, et al. Patterns of colorectal cancer test use, including CT colonography, in the 2010 National Health Interview Survey. Cancer Epidemiol Biomark Prev. 2012;21(6):895–904.
8. Colorectal Cancer Facts & Figures 2017-2019., A.C. Society, Editor. 2017; Atlanta.
9. Gupta S, et al. Comparative effectiveness of fecal immunochemical test outreach, colonoscopy outreach, and usual care for boosting colorectal cancer screening among the underserved: a randomized clinical trial. JAMA Intern Med. 2013;173(18):1725–32.
10. Force, U.S.P.S.T, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315(23):2564–75.
11. Qaseem A, et al. Screening for colorectal cancer: a guidance statement from the American College of Physicians. Ann Intern Med. 2012;156(5):378–86.
12. Wolf AMD, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250–81.
13. Andrews JC, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726–35.
14. Lin JS, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;315(23):2576–94.
15. Huerta S. Recent advances in the molecular diagnosis and prognosis of colorectal cancer. Expert Rev Mol Diagn. 2008;8(3):277–88.
16. Hill MJ, Morson BC, Bussey HJR. Aetiology of adenoma-carcinoma sequence in large bowel. Lancet. 1978;1(8058):245–7.
17. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. NEJM. 1988;319(9):525–32.
18. Winawer SJ. The history of colon cancer screening: a personal perspective. Dig Dis Sci. 2015;60(3):596–608.
19. Gervaz P, Usel M, Rapiti E, Chappuis P, Neyroud-Kaspar I, Bouchardy C. Right colon cancer: left behind. Eur J Surg Oncol. 2016;42(9):1343–9.
20. Committee, A.S.o.P, et al. Complications of colonoscopy. Gastrointest Endosc. 2011;74(4):745–52.
21. CY 2018 Medicare Fee Schedule Changes (National Estimates), C.f.M.a.M. Services, Editor. 2018.
22. Ahlquist DA, et al. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. Clin Gastroenterol Hepatol. 2012;10(3):272–7 e1.
23. Nguyen MT, Weinberg DS. Biomarkers in colorectal cancer screening. J Natl Compr Cancer Netw. 2016;14(8):1033–40.
24. Scholefield JH, et al. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut. 2012;61(7):1036–40.
25. Shaukat A, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013;369(12):1106–14.
26. Allison JE, et al. Population screening for colorectal cancer means getting FIT: the past, present, and future of colorectal cancer screening using the fecal immunochemical test for hemoglobin (FIT). Gut Liver. 2014;8(2):117–30.
27. Church TR, Ederer F, Mandel JS. Fecal occult blood screening in the Minnesota study: sensitivity of the screening test. J Natl Cancer Inst. 1997;89(19):1440–8.
28. Lang CA, Ransohoff DF. Fecal occult blood screening for colorectal cancer. Is mortality reduced by chance selection for screening colonoscopy? JAMA. 1994;271(13):1011–3.
29. Lee JK, et al. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med. 2014;160(3):171.
30. Syngal S, et al. Detection of stool DNA mutations before and after treatment of colorectal neoplasia. Cancer. 2006;106(2):277–83.
31. Bailey JR, Aggarwal A, Imperiale TF. Colorectal cancer screening: stool DNA and other noninvasive modalities. Gut Liver. 2016;10(2):204–11.
32. Imperiale TF, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;370(14):1287–97.
33. Rank KM, Shaukat A. Stool based testing for colorectal cancer: an overview of available evidence. Curr Gastroenterol Rep. 2017;19(8):39.
34. • Prince M, et al. Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. World J Gastroenterol. 2017;23(3):464–71 **An important cross-sectional study with real-world applications demonstrating how a multitarget stool DNA test can significantly improve colorectal cancer screening.**
35. Christofk HR, et al. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. Nature. 2008;452(7184):230–3.
36. Tonus C, et al. Faecal pyruvate kinase isoenzyme type M2 for colorectal cancer screening: a meta-analysis. World J Gastroenterol. 2012;18(30):4004–11.
37. Kim YC, et al. The usefulness of a novel screening kit for colorectal cancer using the immunochromatographic fecal tumor M2 pyruvate kinase test. Gut Liver. 2015;9(5):641–8.
38. Uppara M, et al. A systematic review and meta-analysis of the diagnostic accuracy of pyruvate kinase M2 isoenzymatic assay in diagnosing colorectal cancer. World J Surg Oncol. 2015;13:48.
39. Hoff G, et al. Testing for faecal calprotectin (PhiCal) in the Norwegian Colorectal Cancer Prevention trial on flexible sigmoidoscopy screening: comparison with an immunochemical test for occult blood (FlexSure OBT). Gut. 2004;53(9):1329–33.
40. Widlak MM, et al. Diagnostic accuracy of faecal biomarkers in detecting colorectal cancer and adenoma in symptomatic patients. Aliment Pharmacol Ther. 2017;45(2):354–63.

41. Patel PM, Harris K, Huerta S. Clinical and molecular diagnosis of pathologic complete response in rectal cancer. Expert Rev Mol Diagn. 2015;15(11):1505–16.
42. Ramzan Z, Nassri AB, Huerta S. Genotypic characteristics of resistant tumors to pre-operative ionizing radiation in rectal cancer. World J Gastrointest Oncol. 2014;6(7):194–210.
43. Timmerman C, Taveras LR, Huerta S. Clinical and molecular diagnosis of pathologic complete response in rectal cancer: an update. Expert Rev Mol Diagn. 2018;18(10):887–96.
44. Gupta S, et al. Challenges and possible solutions to colorectal cancer screening for the underserved. J Natl Cancer Inst. 2014;106(4):dju032.
45. Ladabaum U, et al. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomark Prev. 2013;22(9):1567–76.
46. deVos T, et al. Circulating methylated SEPT9 DNA in plasma is a biomarker for colorectal cancer. Clin Chem. 2009;55(7):1337–46.
47. Grutzmann R, et al. Sensitive detection of colorectal cancer in peripheral blood by septin 9 DNA methylation assay. PLoS One. 2008;3(11):e3759.
48. Warren JD, et al. Septin 9 methylated DNA is a sensitive and specific blood test for colorectal cancer. BMC Med. 2011;9:133.
49. Church TR, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut. 2014;63(2):317–25.
50. Chen CH, Yan SL, Yang TH, Chen SF, Yeh YH, Ou JJ, et al. The relationship between the methylated septin-9 DNA blood test and stool occult blood test for diagnosing colorectal cancer in Taiwanese people. J Clin Lab Anal. 2017;31(1). https://doi.org/10.1002/jcla.22013
51. Jin P, et al. Performance of a second-generation methylated SEPT9 test in detecting colorectal neoplasm. J Gastroenterol Hepatol. 2015;30(5):830–3.
52. Nicoloso MS, et al. MicroRNAs—the micro steering wheel of tumour metastases. Nat Rev Cancer. 2009;9(4):293–302.
53. Marshall KW, et al. A blood-based biomarker panel for stratifying current risk for colorectal cancer. Int J Cancer. 2010;126(5):1177–86.
54.• Bray C, et al. Colorectal cancer screening. WMJ. 2017;116(1):27–33 **The development of a risk-stratification tool using molecular testing with exciting implications for streamlined colorectal cancer screening.**
55. Ganepola GA, et al. Use of blood-based biomarkers for early diagnosis and surveillance of colorectal cancer. World J Gastrointest Oncol. 2014;6(4):83–97.
56. Wang S, et al. A plasma microRNA panel for early detection of colorectal cancer. Int J Cancer. 2015;136(1):152–61.
57. Yiu AJ, Yiu CY. Biomarkers in colorectal cancer. Anticancer Res. 2016;36(3):1093–102.
58. Fan C, Lei X, Wu FX. Prediction of CircRNA-disease associations using KATZ model based on heterogeneous networks. Int J Biol Sci. 2018;14(14):1950–9.
59. Chen H, et al. Head-to-head comparison and evaluation of 92 plasma protein biomarkers for early detection of colorectal cancer in a true screening setting. Clin Cancer Res. 2015;21(14):3318–26.
60. Chen H, et al. Prospective evaluation of 64 serum autoantibodies as biomarkers for early detection of colorectal cancer in a true screening setting. Oncotarget. 2016;7(13):16420–32.
61. Issa IA, Noureddine M. Colorectal cancer screening: an updated review of the available options. World J Gastroenterol. 2017;23(28):5086–96.
62. Werner S, et al. Evaluation of a 5-marker blood test for colorectal cancer early detection in a colorectal cancer screening setting. Clin Cancer Res. 2016;22(7):1725–33.
63. Li D. Recent advances in colorectal cancer screening. Chronic Dis Transl Med. 2018;4(3):139–47.
64.•• Check-CapAbbounces FDA Conditional Approval of IDE to Initiate U.S. Pilot Study of C-Scan. 2018 1/4/2019]; Available from: http://ir.check-cap.com/2018-12-13-Check-Cap-Announces-FDA-Conditional-Approval-of-IDE-to-Initiate-U-S-Pilot-Study-of-C-Scan-R **Exciting news announcing the initiation of a pilot study regarding preparation-free capsule-based colorectal cancer screening.**
65. Outsense Toilet IOT Sensor. 1/4/2019]; Available from: https://outsense.co.il/.
66. Hornbrook MC, et al. Early colorectal cancer detected by machine learning model using gender, age, and complete blood count data. Dig Dis Sci. 2017;62(10):2719–27.
67.•• Urban G, et al. Deep learning localizes and identifies polyps in real time with 96% accuracy in screening colonoscopy. Gastroenterology. 2018;155(4):1069–78 e8 **Important machine-learning algorithms to improve polyp detection during colonoscopy, making invasive testing more effective.**
68. DeBourcy AC, et al. Community-based preferences for stool cards versus colonoscopy in colorectal cancer screening. J Gen Intern Med. 2008;23(2):169–74.
69. Ho W, et al. Analysis of barriers to and patients' preferences for CT colonography for colorectal cancer screening in a nonadherent urban population. AJR Am J Roentgenol. 2010;195(2):393–7.
70. Holden DJ, et al. Systematic review: enhancing the use and quality of colorectal cancer screening. Ann Intern Med. 2010;152(10):668–76.
71. Pignone M, Bucholtz D, Harris R. Patient preferences for colon cancer screening. J Gen Intern Med. 1999;14(7):432–7.
72. Ruffin MTt, et al. Factors influencing choices for colorectal cancer screening among previously unscreened African and Caucasian Americans: findings from a triangulation mixed methods investigation. J Community Health. 2009;34(2):79–89.
73. Wolf RL, et al. Patient preferences and adherence to colorectal cancer screening in an urban population. Am J Public Health. 2006;96(5):809–11.
74. Inadomi JM, et al. Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med. 2012;172(7):575–82.